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(54) Title: PROCESS AND INTERMEDIATES FOR THE PREPARATION OF BETA-AMINO ACID AMIDE DIPEPTIDYL PEPTIDASE-IV INHIBITORS

(57) Abstract: A novel process is provided for the preparation of chiral beta-amino acid amide inhibitors of the dipeptidyl peptidase-IV and the useful intermediates obtained therein. The products resulting from the instant process are inhibitors of dipeptidyl peptidase-IV and thereby useful for the treatment of Type 2 diabetes.

WO 2004/087650 A2

TITLE OF THE INVENTION

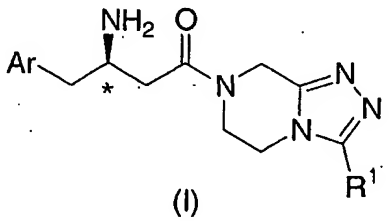
PROCESS AND INTERMEDIATES FOR THE PREPARATION OF BETA-AMINO ACID AMIDE DIPEPTIDYL PEPTIDASE-IV INHIBITORS

FIELD OF THE INVENTION

The present invention relates to a process for the preparation of chiral beta-amino acid amide inhibitors of dipeptidyl peptidase-IV which are useful for the treatment of Type 2 diabetes.

BACKGROUND OF THE INVENTION

The present invention provides an improved process for the preparation of beta-amino acid amide inhibitors of dipeptidyl peptidase-IV of general structural formula I



(I)

having the (*R*)-configuration at the stereogenic center marked with an *; wherein

Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy; and

R^1 is hydrogen or C_{1-4} alkyl unsubstituted or substituted with one to five fluorines.

The present invention also provides structurally novel intermediates useful in the disclosed process.

The compounds of structural formula I, along with their use as inhibitors of dipeptidyl peptidase-IV for the treatment of Type 2 diabetes, were disclosed in WO 03/004498 (published 16 January 2003), which is incorporated by reference herein in its entirety.

WO 03/004498 also described a process for preparing compounds of formula I. However, a large number of synthetic transformations was required with a low overall chemical and optical yield. With the present invention, there are produced more efficiently compounds of structural formula I with an optical purity in excess of 95% in considerably fewer chemical steps with an overall chemical yield of about 45-47% starting from commercially available substituted phenylacetic acids. Moreover, a smaller number of chromatographic purification steps is necessary throughout the synthetic sequence.

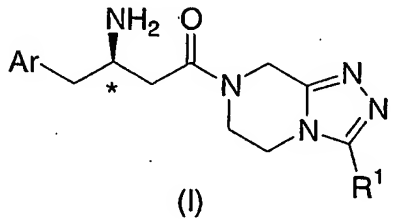
SUMMARY OF THE INVENTION

This invention is concerned with a modular approach for preparing substituted beta-amino acid amide derivatives of structural formula I and certain useful intermediates obtained during that process. The process involves the chiral reduction of a beta-keto ester intermediate to generate a chiral beta-hydroxy ester which is hydrolyzed, converted into a benzyloxyamide and then cyclized to an *N*-benzyloxyazetidinone intermediate. The final steps in the sequence entail saponification of the *N*-benzyloxyazetidinone, amide coupling with a tetrahydrotriazolopyrazine and cleavage of the benzyloxy amine protecting group by hydrogenolysis.

As disclosed in WO 03/004498 (published 16 January 2003), compounds of structural formula I are inhibitors of the enzyme dipeptidyl peptidase-IV (DP-IV) which are useful for the treatment of Type 2 diabetes.

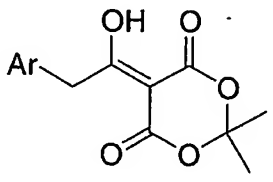
DETAILED DESCRIPTION OF THE INVENTION

The process of the present invention involves the preparation of a chiral compound of structural formula I:



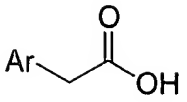
(I)

having the (*R*)-configuration at the stereogenic center marked with an *; wherein
Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy; and
R^1 is hydrogen or C_{1-4} alkyl unsubstituted or substituted with one to five fluorines;
comprising the steps of:
(a) producing a compound of structural formula II:



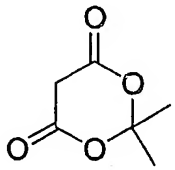
(II)

by treating a phenylacetic acid of structural formula III:



(III)

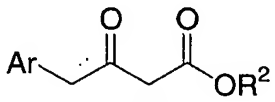
with an acid activating reagent and 2,2-dimethyl-1,3-dioxane-4,6-dione of structural formula IV:



(IV)

in a suitable organic solvent;

(b) producing a compound of structural formula V:

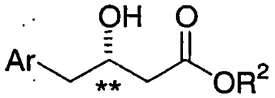


(V)

wherein R^2 is C_{1-6} alkyl;

by treating a compound of structural formula II with a C_{1-6} alkanol;

(c) producing a compound of structural formula VI:

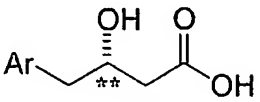


(VI)

having the (*S*)-configuration at the stereogenic center marked with an **;

by treating a compound of structural formula V with an enantioselective reducing agent in a suitable organic solvent;

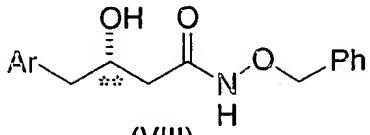
(d) producing a compound of structural formula VII:



(VII)

by treating a compound of structural formula VI with aqueous base;

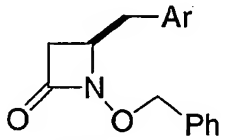
(e) producing a compound of structural formula VIII:



(VIII)

by treating a compound of structural formula VII with benzylhydroxylamine in the presence of a coupling reagent in a suitable reaction solvent;

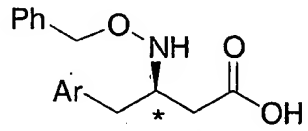
(f) producing a compound of structural formula IX:



(IX)

by cyclocondensing a compound of structural formula VIII with an azodicarboxylate in the presence of a phosphine ligand in a suitable organic solvent;

(g) producing a compound of structural X:

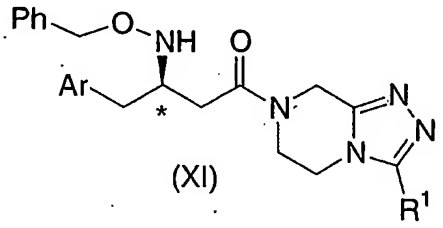


(X)

having the (*R*)-configuration at the stereogenic center marked with an *;

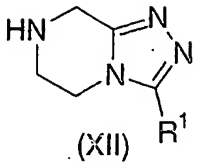
by treating a compound of structural formula IX with aqueous base or aqueous acid;

(h) producing a compound of structural formula XI:



(XI)

by treating a compound of structural formula X with a compound of structural formula XII:



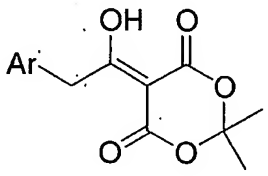
(XII)

or an amine salt thereof, in the presence of a coupling reagent in a suitable organic solvent; and (i) hydrogenolyzing a compound of structural XI in the presence of a palladium catalyst in a suitable organic solvent to afford a compound of structural formula I.

In one embodiment of the process of the present invention, R^1 is CF_3 and Ar is phenyl substituted with one to three substituents independently selected from the group consisting of fluorine, bromine, and trifluoromethyl. In a class of this embodiment Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl.

In another embodiment of the process of the present invention, the final product of the reaction sequence of structural formula I is isolated from the reaction mixture.

The first step in the process of the present invention entails the preparation of a Meldrum's acid adduct of structural formula II:

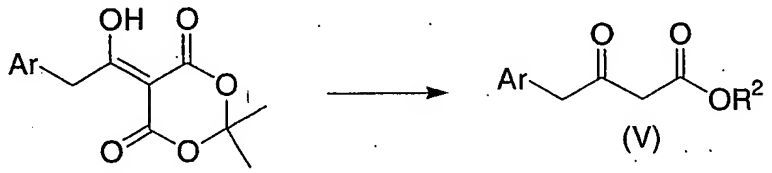


(II)

This is accomplished by treating an appropriately substituted phenylacetic acid with a carboxyl group activating agent to generate an active carboxylic acid species, such as an acyl halide; an active ester, such as an aryl ester; a mixed carboxylic acid anhydride; an acyl imidazole; a mixed carboxylic acid carbonic acid anhydride; and a phosphoric or phosphinic acid mixed anhydride. The activated phenylacetic acid is allowed to react with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) in the presence of base. Formation of the active carboxylic acid species is carried out using methods that are well-known in the practice of organic chemistry. For example, 1,1'-carbonyldiimidazole or 1,1'-thiocarbonyldiimidazole may be used to generate an acyl imidazole; trimethylacetyl (pivaloyl) chloride or isovaleryl chloride to generate a pivalic or isovaleric acid mixed anhydride; oxalyl chloride (in the presence of a catalytic amount of DMF) or phosphorus pentachloride to generate an acid chloride; isobutyl chloroformate to generate an isobutylcarbonic acid mixed anhydride; and diethylcyanophosphate or diethylchlorophosphate to generate a diethylphosphoric acid mixed anhydride. Examples of active aryl esters include *p*-nitrophenyl esters, 2,4-dinitrophenyl esters, and pentafluorophenyl esters. Meldrum's

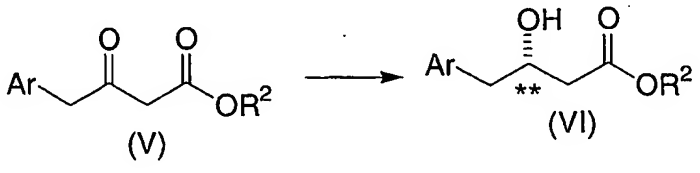
acid may be initially present in the reaction mixture during the formation of the activated acid species or added subsequently after generation of the activated acid species. The reaction is carried out in a suitable organic solvent, such as DCM, DCE, THF, dimethoxymethane, DME, DMF, DMAc, NMP, DMSO, IPAc, EtOAc, MTBE, toluene, MeCN, and propionitrile. If formation of the activated acid species liberates acid, then the reaction is carried out in the presence of base, such as triethylamine, *N,N*-diisopropylethylamine, diisopropylamine, 2,4,6-collidine, imidazole, pyridine, lutidine, *N,N*-dimethylaniline, DMAP, DABCO, and DBU. In one embodiment the Meldrum's acid adduct is prepared using the combination of pivaloyl chloride and DMAP.

The second step in the process of the present invention concerns conversion of a Meldrum's acid adduct of formula II into a beta-keto ester of structural formula V. This is accomplished by alcoholysis with a C_{1-6} alkanol. Preferred alkanols include methanol and ethanol. The reaction is preferably conducted in refluxing methanol.



(II) (V)

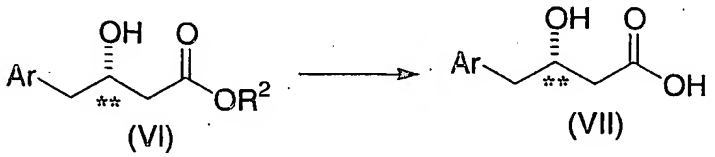
The third step in the process of the present invention involves asymmetric reduction of the beta-keto group in a compound of structural formula V with a chiral reducing agent in a suitable organic solvent to afford a chiral beta-hydroxy ester of structural formula VI. In one embodiment the chiral reduction is effected by Noyori-type asymmetric hydrogenation using [(*S*)-(BINAP-$RuCl_2$)]Et_3N or (*S*)-BINAP-$RuCl_2$ in MeOH as the chiral catalyst [see R. Noyori et al., Angew. Chem. Int. Ed., 40: 40-73 (2001)]. The asymmetric hydrogenation is typically carried out using elevated pressures of hydrogen gas. The chiral beta-hydroxy ester of formula VI is typically obtained in greater than 90% yield and 90% ee. Other chiral catalysts that can also be employed for the asymmetric hydrogenation include (*S*)-[2,2]Phanephos, Duphos, as well as other chiral bisphosphines.



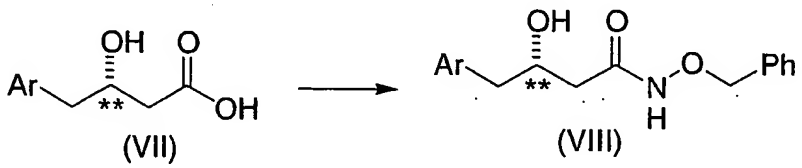
(V) (VI)

The fourth step in the process of the present invention entails hydrolysis of a chiral beta-hydroxy ester of structural formula VI to afford a chiral beta-hydroxy acid of structural formula VII. In one embodiment the hydrolysis is effected under aqueous base conditions with an alkali metal hydroxide,

such as lithium, sodium, and potassium hydroxide; an alkaline earth metal hydroxide, such as barium, calcium, and magnesium hydroxide; or an alkali metal carbonate, such as lithium, sodium, potassium, and cesium carbonate. Solvents that are compatible for the saponification reaction include THF, DME, dioxane, DCE, and toluene all in the presence of water. In one embodiment the organic solvent is aqueous THF.

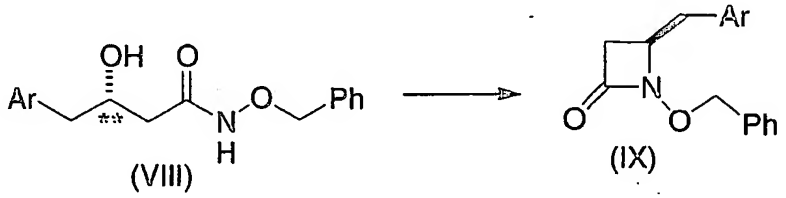


The fifth step in the process of the present invention is conversion of a chiral beta-hydroxy acid of formula VII into a beta-hydroxy benzyloxyamide of structural formula VIII. This is achieved by amide coupling with *O*-benzylhydroxylamine in the presence of a coupling reagent in a suitable solvent. Embodiments of coupling reagents include 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), dicyclohexylcarbodiimide (DCC), 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide, 1,3-di-tert-butylcarbodiimide, 1-(dimethylaminopropyl)-3-ethylcarbodiimide methiodide, 1-tert-butyl-3-(triphenylmethyl)-carbodiimide, 1,3-diisopropylcarbodiimide, bis-(diphenylmethyl)-carbodiimide, 1-tert-butyl-3-ethylcarbodiimide, 1-methyl-2-chloropyridinium iodide, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), BOP-chloride, isobutyl chloroformate, and 1,1'-carbonyldiimidazole. Suitable solvents for the amide coupling reaction include water, THF, MeCN, DMF, DMAc, DCM, ethyl acetate, DCE, IPAc, chloroform, propiontrile, and mixtures thereof. A preferred solvent is water.

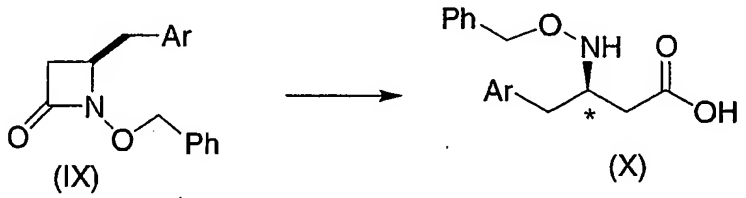


The sixth step in the process of the present invention concerns cyclocondensation of a beta-hydroxy benzyloxyamide of structural formula VIII to generate a beta-lactam or azetidinone of structural formula IX using Mitsunobu reaction conditions. In one embodiment of the Mitsunobu reaction, the azodicarboxylate is a di-(C_{1-4} alkyl) azodicarboxylate, dibenzyl azodicarboxylate, or bis(2,2,2-trichloroethyl) azodicarboxylate. The reaction is performed in the presence of a phosphine ligand, such as a trialkyl- and a triarylphosphine, in a suitable organic solvent. Examples of trialkylphosphines include tributylphosphine and trioctylphosphine. Examples of triarylphosphine include triphenylphosphine and tri(*o*-tolyl)phosphine. Suitable organic solvents for the Mitsunobu

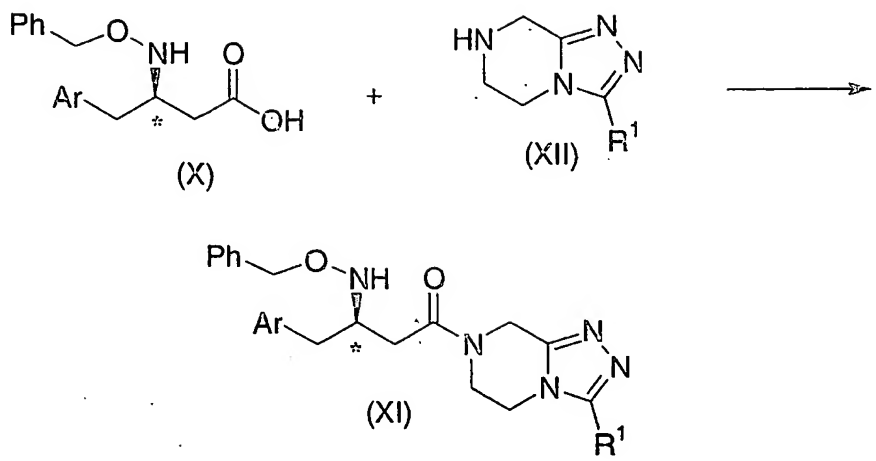
reaction include DCM, chloroform, DCE, toluene, MTBE, THF, EtOAc, IPAc, dimethoxyethane, diethoxyethane, acetonitrile, DMF, xylene, 1,4-dioxane, propionitrile, and mixtures thereof. One embodiment of this step of the process utilizes diisopropyl azodicarboxylate (DIAD) and triphenylphosphine in toluene.



The seventh step in the process of the present invention is hydrolysis of a beta-lactam of structural formula IX to afford a beta-amino acid of structural formula X. The hydrolysis can be effected under either aqueous acid or aqueous base conditions. For hydrolysis under basic conditions, an alkali metal hydroxide, such as lithium, sodium, and potassium hydroxide; an alkaline earth metal hydroxide, such as barium, calcium, and magnesium hydroxide; or an alkali metal carbonate, such as lithium, sodium, potassium, and cesium carbonate, can be used. Solvents that are compatible for the saponification reaction include THF, DME, dioxane, DCE, and toluene, all in the presence of water. In one embodiment the organic solvent is miscible with water. The hydrolysis can also be performed by heating a beta-lactam of formula IX with aqueous acid in methanol, such as aqueous hydrochloric acid and aqueous sulfuric acid.



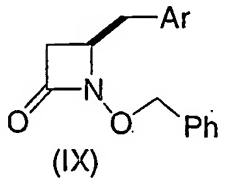
The penultimate step in the process of the present invention is amide coupling of a beta-amino acid of structural formula X with a tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine of structural formula XII or an amine salt thereof in the presence of a coupling reagent in a suitable organic solvent to afford a beta-amino acid amide of structural formula XI. The scope and ranges of conditions that can be employed for the amide coupling reaction are similar to those for the conversion of VII into VIII. In one embodiment, the coupling reaction is performed using EDC in the presence of *N*-methylmorpholine in acetonitrile or DMF or an aqueous mixture thereof.



The final step in the process of the present invention is removal of the benzyloxy protecting group on the amine functionality of a compound of structural formula XI. This is accomplished under hydrogenolytic conditions in the presence of a metal catalyst in an organic solvent. Suitable organic solvents for the hydrogenolysis include, but are not limited to, a lower alkanol, such as methanol, ethanol, and isopropyl alcohol; THF, DME, diethoxyethane, and IPAc, and aqueous mixtures thereof. IPAc can also be used with an additive, such as HCl, HBr, acetic acid, and formic acid. Transfer hydrogenation conditions can also be employed wherein the hydrogen is generated *in situ*. Sources of hydrogen for the transfer hydrogenation include ammonium formate, formic acid, cyclohexene, and isopropyl alcohol. Metal catalysts include Pd/C, Pd/Al_2O_3, $Pd/CaCO_3$, and $Pd(OH)_2/C$. Other catalysts can also be used such as Pt, Rh, and Ni based catalysts, or oxides thereof, alone or on supports such as carbon, silica, and alumina. In one embodiment the hydrogenolysis is carried out with 10% Pd/C as catalyst in methanol as the solvent.

The process steps can be carried out without the need for isolating the intermediates of structural formulae II to XI.

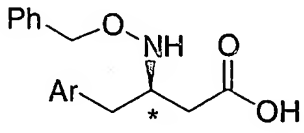
A further embodiment of the present invention comprises the following novel compounds of structural formula IX which are intermediates in the preparation of the compounds of structural formula I:



(IX)

wherein Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy. In one embodiment of the novel intermediates of structural formula IX, Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl.

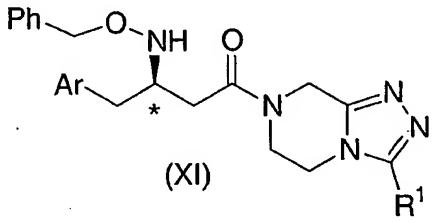
A further embodiment of the present invention comprises the following novel compounds of structural formula X which are intermediates in the preparation of the compounds of structural formula I:



(X)

wherein Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy. In one embodiment of the novel intermediates of structural formula X, Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl.

A further embodiment of the present invention comprises the following novel compounds of structural formula XI which are intermediates in the preparation of the compounds of structural formula I:



(XI)

wherein Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy; and R^1 is hydrogen or C_{1-4} alkyl unsubstituted or substituted with one to five fluorines. In one embodiment of the novel intermediates of structural formula XI, Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl and R^1 is trifluoromethyl.

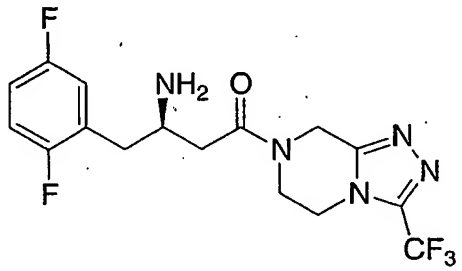
Representative experimental procedures utilizing the novel process are detailed below. For purposes of illustration, the following Examples are directed to the preparation of compound 2-3 and 2-10 but doing so are not intended to limit the process of the present invention to the specific conditions for making these particular compounds.

Abbreviations: DABCO is 1,4-diazabicyclo[2.2.2]octane; DBU is 1,8-diazabicyclo[5.4.0]undec-5-ene; DCE is 1,2-dichloroethane; DCM is dichloromethane; DMAc is *N,N*-dimethylacetamide; DMAP is 4-(dimethylamino)pyridine; DME is 1,2-dimethoxyethane; DMF is *N,N*-dimethylformamide; EtOAc is ethyl acetate; EtOH is ethanol; HPLC is high-performance liquid chromatography; IPAc is isopropyl acetate; MeCN is acetonitrile; MeOH is methanol; MTBE is methyl *t*-butyl ether; NMM is *N*-methylmorpholine; NMP is *N*-methylpyrrolidinone; PPh_3 is triphenylphosphine; and THF is tetrahydrofuran.

By halogen is meant fluorine, chlorine, bromine, or iodine.

The starting materials are either commercially available or known in the chemical scientific or patent literature. Purification procedures include e.g., distillation, crystallization and normal or reverse phase liquid chromatography.

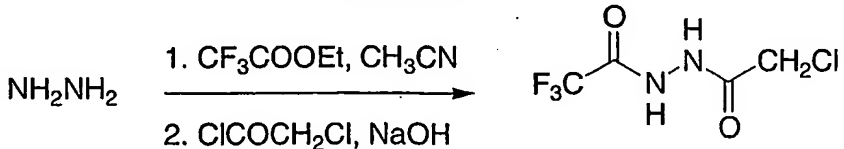
EXAMPLE 1



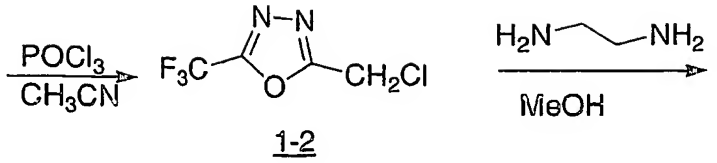
(2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,5-difluorophenyl)butan-2-amine (2-10)

Preparation of 3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine, hydrochloride salt (1-4)

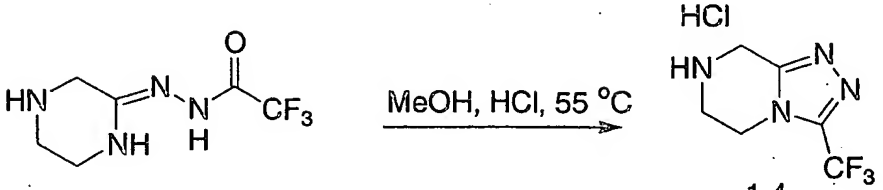
Scheme 1



1-1



1-2



1-3 1-4

Step A: Preparation of bishydrazide (1-1)

Hydrazine (20.1 g, 35 wt% in water, 0.22 mol) was mixed with 310 mL of acetonitrile. 31.5 g of ethyl trifluoroacetate (0.22 mol) was added over 60 min. The internal temperature was increased to 25 °C from 14 °C. The resulting solution was aged at 22 - 25 °C for 60 min. The solution was cooled to 7 °C. 17.9 g of 50 wt% aqueous NaOH (0.22 mol) and 25.3 g of chloroacetyl chloride (0.22 mol) were added simultaneously over 130 min at a temperature below 16 °C. When the reaction was complete, the mixture was vacuum distilled to remove water and ethanol at 27 ~ 30 °C and under 26 ~ 27 in Hg vacuum. During the distillation, 720 mL of acetonitrile was added slowly to maintain constant volume (approximately 500 mL). The slurry was filtered to remove sodium chloride. The cake was rinsed with about 100 mL of acetonitrile. Removal of the solvent afforded bis-hydrazide 1-1 (43.2 g, 96.5% yield, 94.4 area% pure by HPLC assay).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 4.2 (s, 2H), 10.7 (s, 1H), and 11.6 (s, 1H) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6): δ 41.0, 116.1 (q, J = 362 Hz), 155.8 (q, J = 50 Hz), and 165.4 ppm.

Step B: Preparation of 5-(trifluoromethyl)-2-(chloromethyl)-1,3,4-oxadiazole (1-2)

Bishydrazide 1-1 from Step A (43.2 g, 0.21 mol) in ACN (82 mL) was cooled to 5 °C. Phosphorus oxychloride (32.2 g, 0.21 mol) was added, maintaining the temperature below 10 °C. The mixture was heated to 80 °C and aged at this temperature for 24 h until HPLC showed less than 2 area% of 1-1. In a separate vessel, 260 mL of IPAc and 250 mL of water were mixed and cooled to 0 °C. The reaction slurry was charged to the quench keeping the internal temperature below 10 °C. After the addition, the mixture was agitated vigorously for 30 min, the temperature was increased to room temperature and the aqueous layer was cut. The organic layer was then washed with 215 mL of water, 215 mL of 5 wt% aqueous sodium bicarbonate and finally 215 mL of 20 wt% aqueous brine solution. HPLC assay yield after work up was 86-92%. Volatiles were removed by distillation at 75-80 mm Hg,

55 °C to afford an oil which could be used directly in Step C without further purification. Otherwise the product can be purified by distillation to afford 1-2 in 70-80% yield.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.8 (s, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ 32.1, 115.8 (q, J = 337 Hz), 156.2 (q, J = 50 Hz), and 164.4 ppm.

Step C: Preparation of N-[(2Z)-piperazin-2-ylidene]trifluoroacetohydrazide (1-3)

To a solution of ethylenediamine (33.1 g, 0.55 mol) in methanol (150 mL) cooled at –20 °C was added distilled oxadiazole 1-2 from Step B (29.8 g, 0.16 mol) while keeping the internal temperature at –20 °C. After the addition was complete, the resulting slurry was aged at –20 °C for 1 h. Ethanol (225 mL) was then charged and the slurry slowly warmed to –5 °C. After 60 min at –5 °C, the slurry was filtered and washed with ethanol (60 mL) at –5 °C. Amidine 1-3 was obtained as a white solid in 72% yield (24.4 g, 99.5 area wt% pure by HPLC).

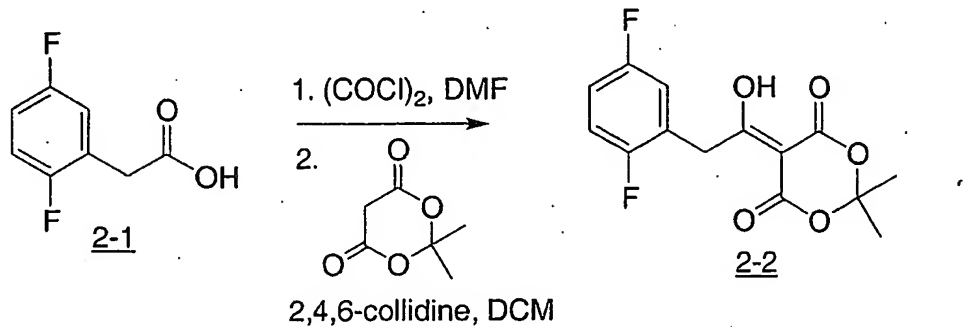
^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.9 (t, 2H), 3.2 (t, 2H), 3.6 (s, 2H), and 8.3 (b, 1H) ppm. ^{13}C-NMR (100 MHz, DMSO-d_6): δ 40.8, 42.0, 43.3, 119.3 (q, J = 350 Hz), 154.2, and 156.2 (q, J = 38 Hz) ppm.

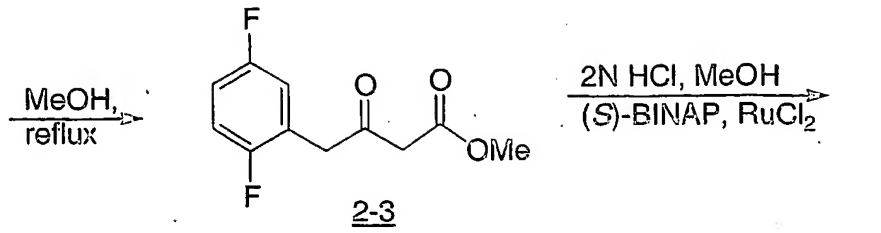
Step D: Preparation of 3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine, hydrochloride salt (1-4)

A suspension of amidine 1-3 (27.3 g, 0.13 mol) in 110 mL of methanol was warmed to 55 °C. 37% Hydrochloric acid (11.2 mL, 0.14 mol) was added over 15 min at this temperature. During the addition, all solids dissolved resulting in a clear solution. The reaction was aged for 30 min. The solution was cooled down to 20 °C and aged at this temperature until a seed bed formed (10 min to 1 h). 300 mL of MTBE was charged at 20 °C over 1 h. The resulting slurry was cooled to 2 °C, aged for 30 min and filtered. Solids were washed with 50 mL of ethanol:MTBE (1:3) and dried under vacuum at 45 °C. Yield of triazole 1-4 was 26.7 g (99.5 area wt% pure by HPLC).

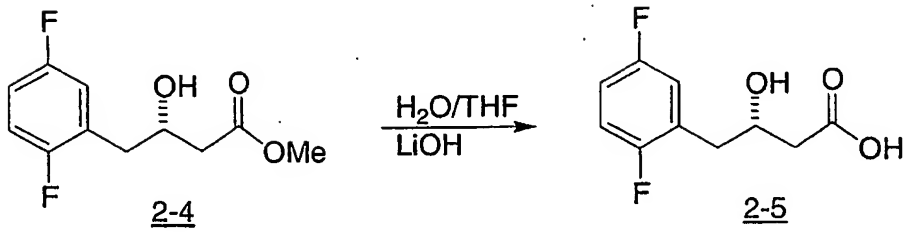
^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.6 (t, 2H), 4.4 (t, 2H), 4.6 (s, 2H), and 10.6 (b, 2H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ: 39.4, 39.6, 41.0, 118.6 (q, J = 325 Hz), 142.9 (q, J = 50 Hz), and 148.8 ppm.

Scheme 2

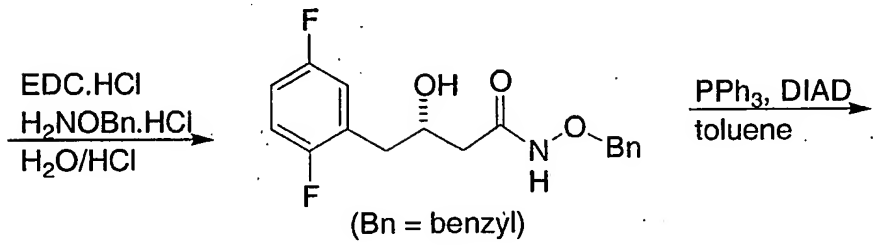




2-3

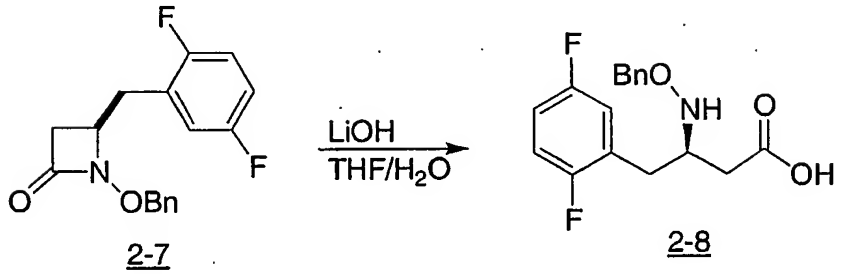


2-4 2-5

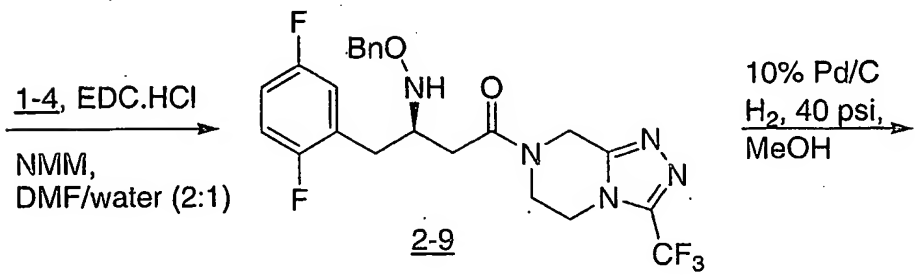


(Bn = benzyl)

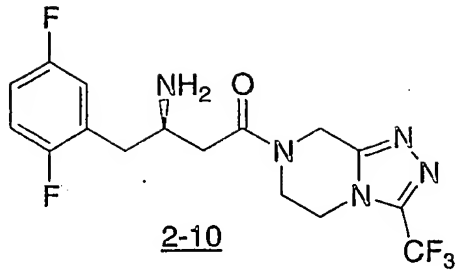
2-6



2-7 2-8



2-9



2-10

Step A: Preparation of 5-[1-hydroxy-2-(2,5-difluorophenyl)ethylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (2-2)

Oxalyl chloride (2.54 Kg, 1.72 L, 20.1 mol) was slowly added to a slurry of 2,5-difluorophenylacetic acid (3.00 Kg, 17.4 mol) and DMF (9 mL) in dichloromethane (11 L) at 25-30 °C over 1.5 h. The mixture was stirred for 2 h at room temperature until the end of HCl gas evolution. Dichloromethane and excess $(COCl)_2$ were distilled off (20-25 °C, 28" Hg). Dichloromethane (2 L) was added to the residue and the resulting solution was then slowly added to a mixture of Meldrum's acid (2.64 Kg, 18.3 mol) and sym-collidine (4.22 Kg, 4.6 L, 34.9 mol) in dichloromethane (18 L) at –5 °C over 2 h. The resulting pale yellow solution was stirred 1 h at 0 °C. Then 10.4 L of 6M HCl was charged at 0 °C over 5 min. The layers were separated and the organic layer was extracted with 69 L of 1 M NaOH, then with 34 L of 1 M NaOH. The combined basic aqueous layers were acidified with 37% HCl (approx. 8.5 L) until pH=1. The solid was filtered off and washed with water (30-50 L) then dried under a stream of nitrogen for 5 days to yield 4.3 Kg (83%) of Meldrum's acid adduct 2-2.
mp 89-91 °C. ^{1}H NMR ($CDCl_3$): 1.77 (s, 6H), 4.49 (s, 2H), 6.95-7.07 (m, 3H).
^{13}C NMR: 26.9, 35.1, 91.9, 105.4, 115.8 dd, 116.4 dd, 118.0 dd, 122.6 dd, 156.8 d, 159.2 d, 160.3, 170.5, 193.0. IR: 1204.5, 1425.6, 1498.4, 1579.0, 1736.2, 2848.6, 2922.0. Calcd for $C_{14}H_{12}F_2O_5$: C, 56.38; H, 4.06; F, 12.74. Found: C, 56.13; H, 3.66; F, 13.04.

Step B: Preparation of methyl 4-(2,5-difluorophenyl)-3-oxobutanoate (2-3)

A solution of Meldrum's acid adduct 2-2 (4.27 Kg) was refluxed in anhydrous methanol (20 L) for 2.5 h. The methanol was evaporated (20-25 °C, 28 " Hg) and MTBE (10 L) was added to the oily residue (ca 5 L). The resulting solution was filtered through a plug of silica gel (1500 g) and washed with 6 L of MTBE. The MTBE was evaporated (20-25 °C, 28 " Hg) and 22 L of methanol was added to the oily residue (ca 5 L). Quantitative HPLC analysis indicated 2.97 Kg (91%) assay yield in the final MeOH solution. Evaporation of a sample to dryness gave the ketoester 2-3 as a crystalline solid: mp 37-39 °C.

^{1}H NMR ($CDCl_3$): δ 3.50 (s, 2H), 3.69 (s, 3H), 3.83 (d, 2H), 6.86-6.94 (m, 2H), 6.94-7.00 (m, 1H). enol form: 3.48 (s), 3.67 (s), 12.04 (s).
^{13}C NMR: δ 42.7, 48.3, 52.3, 115.5 dd, 116.3 dd, 118.1 dd, 122.3 dd, 172.8, 198.3. IR: 1014.7, 1497.1, 1716.8, 2956.8. Calcd for $C_{11}H_{10}F_2O_3$: C, 57.90; H, 4.42; F, 16.65. Found: C, 57.69; H, 4.11; F, 16.56.
HPLC RT: 14.64 mn

Step C: Preparation of methyl (3*S*)-4-(2,5-difluorophenyl)-3-hydroxybutanoate (2-4)

The solution from Step B was divided into 2 batches (approx. 12 L each) and degassed by bubbling in N_2 for 15 min. 2N HCl (70 mL) and then (*S*)-BINAP-$RuCl_2$ (22.3 g, 0.4 mol%) were added to each batch which was then submitted to hydrogenation (H_2, 150 psi, 5 gal autoclave) at 60 °C for 4-5 h. Both batches were then combined and further processed as described in Step D.

Step D: Preparation of (3*S*)-4-(2,5-difluorophenyl)-3-hydroxybutanoic acid (2-5)

The methanol solution of β-hydroxyester from Step C was solvent switched to THF (17 L final volume) using 35 L of THF with a minimal residual volume of 5 L (20-25 °C, 28 " Hg). A solution of $LiOH.H_2O$ (2.37 kg, 56.5 mol) in water (12 L) was added at 20-25 °C to the preceding mixture. The solution was stirred for 30 min, MTBE (8 L) was then added and the layers separated. The aqueous layer was extracted with MTBE (2 x 8 L) then the combined organic layers were back-extracted with water (8 L). The combined aqueous layers were used directly in Step E below.

Step E: Preparation of (3*S*)-N-(benzyloxy)-4-(2,5-difluorophenyl)-3-hydroxybutanamide (2-6)

To the aqueous solution from Step D was added 37% aqueous HCl (3.5 L, 42 mol) then O-benzylhydroxylamine hydrochloride (2.71 kg, 16.9 mol) followed by slow addition of EDC.HCl (4.06 kg, 21.2 mol) over 15 min at 20-30 °C. The resulting mixture was stirred for 1 h at 20-22 °C while the hydroxamate precipitated. The light pink solid was filtered off and washed with water (3 x 12 L) and with heptane (3 x 12 L), then dried over a stream of nitrogen gas for 3 d (yield 4.27 Kg).
Chiral HPLC (AR) indicated 92% ee.
Specific rotation $[\alpha]_{589} = +12.96°$
HPLC RT: 13.95 min
MP: 70-72 °C. IR: 1495.9, 1653.1, 2847.8, 3214.6. Calcd for $C_{17}H_{17}F_2NO_3$: C, 63.54; H, 5.33; F, 16.65; N, 4.36. Found: C, 63.59; H, 5.04; F, 12.01; N, 4.32.

Step F: Preparation of (4*R*)-1-(benzyloxy)-4-(2,5-difluorobenzyl)azetidin-2-one (2-7)

Triphenylphosphine (3.64 kg, 13.9 mol) was slowly added to a solution of diisopropyl azodicarboxylate (2.80 kg, 2.73 L, 13.9 mol) in toluene (43 L) at such a rate that the temperature did not

rise above 25 °C over 30 min. The β-hydroxamate from Step E (4.05 kg, 12.6 mol) was then added portionwise at 20-30 °C over 30 min. After 2 h at 20-22 °C, 12-15 A% of starting hydroxamate remained (HPLC). A solution was prepared from triphenylphosphine (364 g) and DIAD (280 g) in toluene (4.3 L) as described above. This solution was then added to the reaction mixture at 20-22 °C over 5 min and the resulting solution stirred for a further 1 h. The solid was filtered off and the filter cake was washed with 5 L of toluene. The filtrates were solvent switched to methanol (final volume 20 L) using 35 L of methanol (20-25 °C, 28 " Hg). The solution was cooled to –30 °C for 30 min while the product crystallized out. The slurry was then filtered and the white crystals washed with cold methanol/water 9:1 (4 x 8 L, -50 °C). The solid was dried overnight under a stream of nitrogen gas (yield 3.00 Kg). Chiral HPLC (AR) indicated 99.7% ee; Specific rotation $[\alpha]_{589} = +9.24°$

HPLC RT: 17.4 min.

MP: 80 °C. ^{13}C NMR: 31.8, 37.9, 57.2, 78.3, 115.1 dd, 116.5 dd, 117.6 dd, 125.2 dd, 128.7, 129.1, 129.3, 156.7 d, 159.1 d, 163.9. IR: 728.8, 1043.3, 1496.7, 1774.4. Calcd for $C_{17}H_{15}F_2NO_2$: C, 67.32; H, 4.98; F, 12.53; N, 4.62. Found: C, 67.22; H, 4.80; F, 12.66; N, 4.68.

Step G: Preparation of (3*R*)-3-[(benzyloxy)amino]-4-(2,5-difluorophenyl)butanoic acid (2-8)

A 4-neck, 72 L round-bottom flask which was equipped with a mechanical stirrer, N_2 inlet and thermocouple, was charged with the *N*-benzyloxy-β-lactam from Step F (2.66 kg) and THF. Lithium hydroxide solution (0.55 kg of $LiOH.H_2O$ in 8.8 L of water) was charged at 10-20 °C over a period of 20 min. The resulting mixture was aged at ambient temperature for 1-2 h (or overnight at about 18-20°C). The end of reaction was monitored by HPLC (>99.5% conversion). Then, THF was distilled off under vacuum at 5-20 °C. After distillation of THF, methanesulfonic acid was added at a temperature below 23°C to adjust the pH of the remaining aqueous solution (pH about 3-4). During this time, the product was precipitated. Then, DMF (9.9 L) was charged slowly with ice-bath cooling (exothermic) to dissolve the precipitate. The resulting homogeneous solution was used directly in Step H below.

Step H: Preparation of 7-[(3*R*)-3-[(benzyloxy)amino]-4-(2,5-difluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine (2-9)

To a solution of the product from Step G in DMF/water (2:1) was added triazole HCl salt 1-4 (2.51 kg, 11.0 mol) at about 18-23°C. After aging for 15 min, the homogeneous solution was cooled to 10°C. Then, NMM (0.89 kg, 8.77 mol) was added at 10-18 °C. After aging the resulting solution for 10 min, EDC-HCl salt (2.52 kg, 13.2 mol) was charged at –2 °C to 0 °C over 30 min, and aged for 30 min at this temperature. Additional NMM (0.1 eq) was then added. The reaction mixture was aged for 2 h at 0 °C. Then, EtOAc (30 L) and water (19.8 L) were charged sequentially. After separation of the layers, the organic layer was washed with 10% brine (4 x 21 L). The organic layer was batch concentrated and

solvent switched to methanol. The final volume of methanol solution was adjusted to 20 L for the hydrogenolysis step I below.

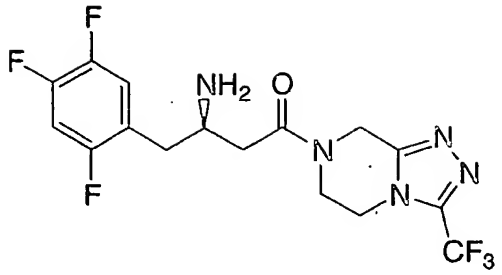
Step I: Preparation of (2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,5-difluorophenyl)butan-2-amine (2-10)

Hydrogenation was done in 2-batches in the 5 gallon autoclave using total 440 g 10% Pd/C at 40 psi at 60 °C for 16 h. The crude solution was filtered through Solka-floc (1.5 kg, pre-washed with MeOH, ~15 L), and rinsed with 10 L of MeOH. The resulting solution was batch concentrated in a 72 L round-bottom flask and the final volume of solution was adjusted to 26 L. (L)-Tartaric acid (1.11 Kg) and IPA (41 L) were placed in 100 L round-bottom flask, and the resulting slurry was heated to ~ 65°C (until homogenous solution). The methanol solution of free amine (26 L) was added to the tartaric acid solution dropwise keeping temperature at about 60-65 °C. The precipitated crystalline salt was aged for 30 min at this temperature and cooled gradually to 0°C with efficient stirring. After aging for 1 h at 0 °C, the crude salt was filtered off and rinsed with 3 L of 2:1 iPA-MeOH (pre-cooled to 0°C). The cake was dried in a filter pot under reduced pressure with a nitrogen sweep for 16 h to give the crude tartrate as a white crystalline solid (3.97 Kg).

The crude (L)-tartaric acid salt (2.0 Kg) was dissolved in 50 L of MeOH at reflux temperature (about 59°C). The homogenous solution was cooled to 45 °C and transferred to a 100 L round-bottom flask through an in-line filter. About 5 L of methanol was distilled off. The solution was heated to about 50-55°C and IPA (43 L) was charged (in-line filter) slowly over 30 min keeping the temperature at about 55-65°C. After aging the slurry for 1 h at about 60-65°C, the slurry was gradually cooled to 0 °C with efficient stirring. After aging for 1 h, the product was filtered off and rinsed with 3 L of 1:1 iPA:MeOH (pre-cooled to 0°C). The cake was dried in filter pot under reduced pressure with nitrogen sweep for 2 d to give white crystalline tartaric acid salt (1.75 kg, 99.8 A%). A total of 3.58 kg of the pure tartaric acid salt was obtained in 75 % overall yield from two batches from the lactam intermediate 2-7.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.5~ 6.8, 6 H; 7.24~ 7.02, 3H; 4.96~ 4.77, 2H; 4.24~4.18 1H; 4.01~ 3.86, 2H; 3.91, 2H; 2.96-2.64, 4H.

EXAMPLE 2



(2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine

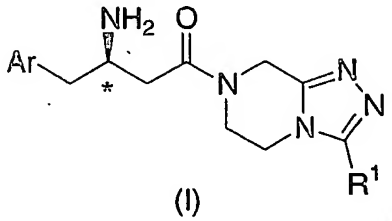
This compound was prepared in a similar fashion as Example 1, but using commercially available 2,4,5-trifluorophenylacetic acid in place of 2,5-difluorophenylacetic acid in Step A. Melting point 114.1 – 115.7 °C.

^{1}H NMR (300 MHz, CD_3CN): δ 7.26 (m), 7.08 (m), 4.90 (s), 4.89 (s), 4.14 (m), 3.95 (m), 3.40 (m), 2.68 (m), 2.49 (m), 1.40 (bs).

^{13}C NMR (CD_3CN): δ 171.8, 157.4 (ddd , J_{CF} = 242.4, 9.2, 2.5 Hz), 152.2 (major), 151.8 (minor), 149.3 (ddd; J_{CF} = 246.7, 14.2, 12.9 Hz), 147.4 (ddd, J_{CF} = 241.2, 12.3, 3.7 Hz), 144.2 (q, J_{CF} = 38.8 Hz), 124.6 (ddd , J_{CF} = 18.5, 5.9, 4.0 Hz), 120.4 (dd , J_{CF} = 19.1, 6.2 Hz), 119.8 (q, J_{CF} = 268.9 Hz), 106.2 (dd , J_{CF} = 29.5, 20.9 Hz), 50.1, 44.8, 44.3 (minor), 43.2 (minor), 42.4, 41.6 (minor), 41.4, 39.6, 38.5 (minor), 36.9.

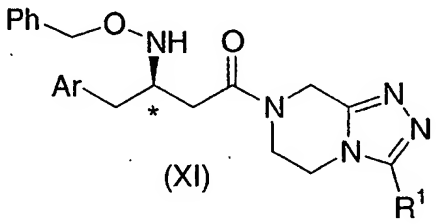
WHAT IS CLAIMED IS:

1. A process for preparing a compound of structural formula I:



(I)

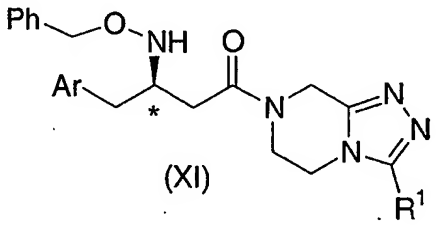
having the (*R*)-configuration at the stereogenic center marked with an *; wherein
Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy; and
R^1 is hydrogen or C_{1-4} alkyl unsubstituted or substituted with one to five fluorines;
comprising the step of hydrogenolyzing a compound of structural XI:



(XI)

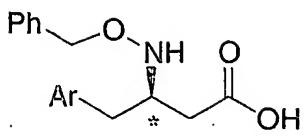
in the presence of a palladium catalyst in a suitable organic solvent.

2. The process of Claim 1 additionally comprising the step of producing a compound of structural formula XI:



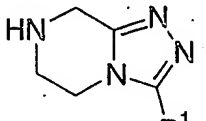
(XI)

by treating a compound of structural formula X:



(X)

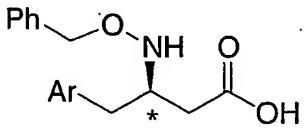
with a compound of structural formula XII:



(XII)

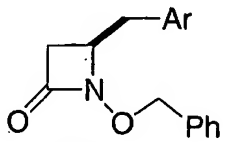
or an amine salt thereof, in the presence of a coupling reagent in a suitable organic solvent.

3. The process of Claim 2 additionally comprising the step of producing a compound of structural formula X:



(X)

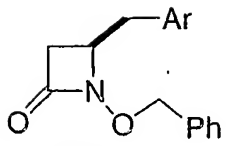
having the (*R*)-configuration at the stereogenic center marked with an *;
by treating a compound of structural formula IX:



(IX)

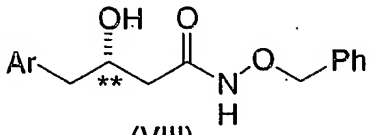
with aqueous base or aqueous acid.

4. The process of Claim 3 additionally comprising the step of producing a compound of structural formula IX:



(IX)

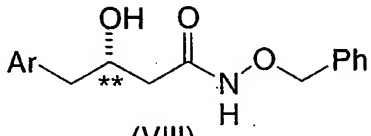
by cyclocondensing a compound of structural formula VIII:



(VIII)

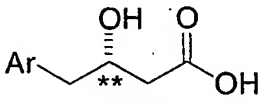
with an azodicarboxylate in the presence of a phosphine ligand in a suitable organic solvent.

5. The process of Claim 4 additionally comprising the step of producing a compound of structural formula VIII:



(VIII)

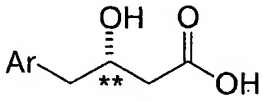
by treating a compound of structural formula VII:



(VII)

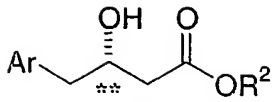
with benzylhydroxylamine in the presence of a coupling reagent in a suitable reaction solvent.

6. The process of Claim 5 additionally comprising the step of producing a compound of structural formula VII:



(VII)

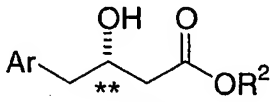
by treating a compound of structural formula VI:



(VI)

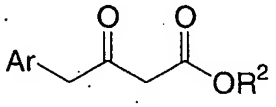
wherein R^2 is C_{1-6} alkyl, with aqueous base.

7. The process of Claim 6 additionally comprising the step of producing a compound of structural formula VI:



(VI)

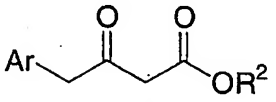
having the (*S*)-configuration at the stereogenic center marked with an **;
by treating a compound of structural formula V:



(V)

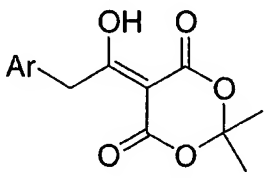
with an enantioselective reducing agent in a suitable organic solvent.

8. The process of Claim 7 additionally comprising the step of producing a compound of structural formula V:



(V)

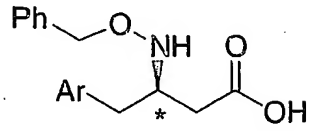
by treating a compound of structural formula II:



(II)

with a C_{1-6} alkanol.

9. A compound of structural formula X:

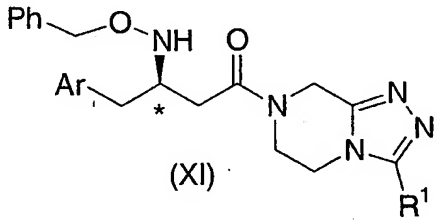


(X)

wherein Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy.

10. The compound of Claim 9 wherein Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl.

11. A compound of structural formula XI:

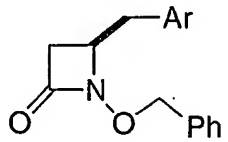


(XI)

wherein Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy; and R^1 is hydrogen or C_{1-4} alkyl unsubstituted or substituted with one to five fluorines.

12. The compound of Claim 11 wherein Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl and R^1 is trifluoromethyl.

13. A compound of structural formula IX:

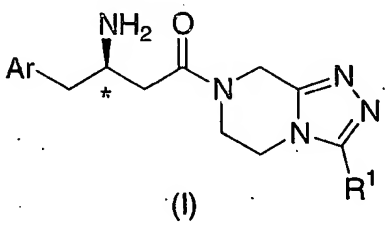


(IX)

wherein Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy.

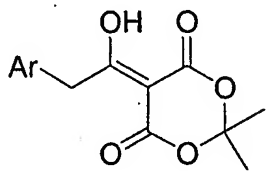
14. The compound of Claim 13 wherein Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl.

15. A process for preparing a compound of structural formula I:



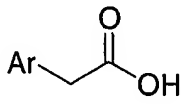
(I)

having the (*R*)-configuration at the stereogenic center marked with an *; wherein
Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy; and
R^1 is hydrogen or C_{1-4} alkyl unsubstituted or substituted with one to five fluorines;
comprising the steps of:
(a) producing a compound of structural formula II:



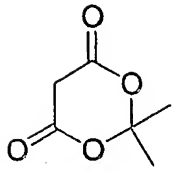
(II)

by treating a phenylacetic acid of structural formula III:



(III)

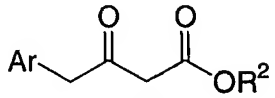
with an acid activating reagent and 2,2-dimethyl-1,3-dioxane-4,6-dione of structural formula IV:



(IV)

in a suitable organic solvent;

(b) producing a compound of structural formula V:

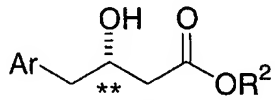


(V)

wherein R^2 is C_{1-6} alkyl;

by treating a compound of structural formula II with a C_{1-6} alkanol;

(c) producing a compound of structural formula VI:

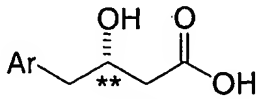


(VI)

having the (*S*)-configuration at the stereogenic center marked with an **;

by treating a compound of structural formula V with an enantioselective reducing agent in a suitable organic solvent;

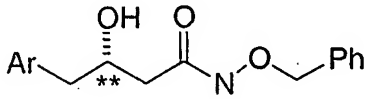
(d) producing a compound of structural formula VII:



(VII)

by treating a compound of structural formula VI with aqueous base;

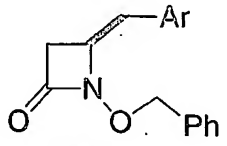
(e) producing a compound of structural formula VIII:



(VIII)

by treating a compound of structural formula VII with benzylhydroxylamine in the presence of a coupling reagent in a suitable reaction solvent;

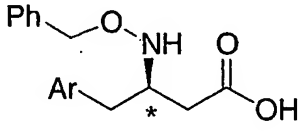
(f) producing a compound of structural formula IX:



(IX)

by cyclocondensing a compound of structural formula VIII with an azodicarboxylate in the presence of a phosphine ligand in a suitable organic solvent;

(g) producing a compound of structural X:

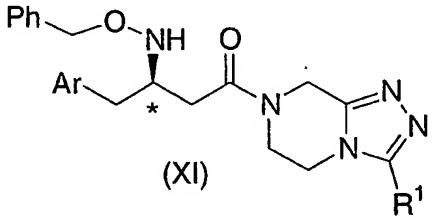


(X)

having the (*R*)-configuration at the stereogenic center marked with an *;

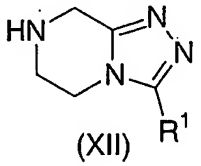
by treating a compound of structural formula IX with aqueous base or aqueous acid;

(h) producing a compound of structural formula XI:



(XI)

by treating a compound of structural formula X with a compound of structural formula XII:



(XII)

or an amine salt thereof, in the presence of a coupling reagent in a suitable organic solvent; and

(i) hydrogenolyzing a compound of structural XI in the presence of a palladium catalyst in a suitable organic solvent to afford a compound of structural formula I.